



In response to the November 29, 2001 Notice to File Corrected Application Papers in the above-identified application, please amend the application as follows:

**In the Specification**

1. On page 13, please add the following new paragraphs after line 15:

**BRIEF DESCRIPTION OF THE DRAWINGS**

Figure 1A shows the effect of the positive isomer of the delta agonist BW373U86 on respiratory depression induced by the mu agonist, alfenta.

Figure 1B shows the effect of the delta agonist BW373U86 on analgesia induced by the mu agonist, alfenta.

B1  
Figure 2A shows the analgesic and respiratory depression effects of 3290W93 and fentanyl in rats, plotted at 4 minute time points at which times peak effects were observed following drug administration.

Figure 2B shows the analgesic and respiratory depression effects of 3290W93 and fentanyl in rats, plotted at 8 minute time points.

2. On page 66, please replace the paragraph beginning at line 4, with the following paragraph:

As an indication of respiratory depression, blood CO<sub>2</sub> levels were observed to increase as a result of alfenta administration. The key finding in the experiment, however, was that BW373U86 dose dependently reduced the level of pCO<sub>2</sub> seen following the alfenta infusion. Results are depicted in Figures 1A and 1B.

3. On page 66, please replace the paragraph beginning at line 9, with the following paragraph:

h2  
Figures 1A and 1B show the effect of the positive isomer of the delta agonist BW373U86 on analgesia and respiratory depression induced by the mu agonist, alfenta. (+)373U86 blocks the respiratory depression (as shown by Fig. 1A), but not the analgesia induced by alfenta (as shown by Fig. 1B). The negative isomer of 373U86 does not have any significant effects on alfenta-induced respiratory

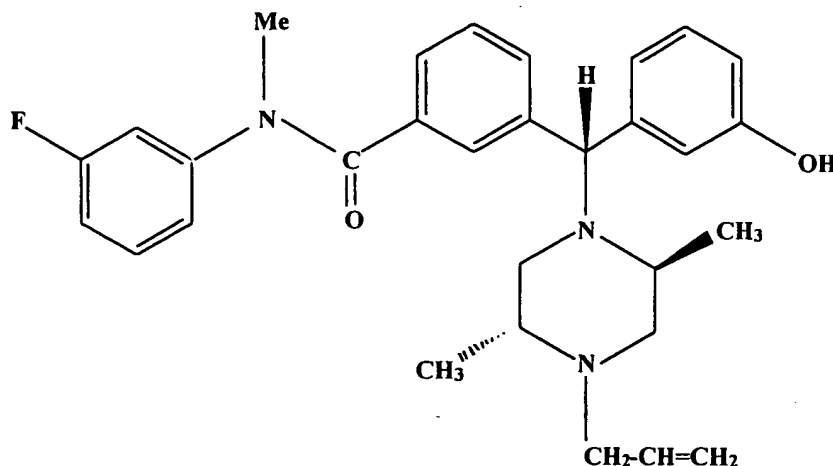
hmo<sup>1</sup> depression (data not shown). All doses of BW373U86 are plotted in the analgesia graph, however some points cannot be seen because the symbols are overlapping.

4. On page 66, please replace the paragraph beginning at line 16, with the following paragraph:

B3 Analgesia was also assessed with a tail-pinch method at the same time points that blood was drawn. Most importantly, BW373U86 did not significantly affect the analgesia produced by alfenta (Fig. 1B). Overall, the data indicate that BW373U86, or other delta agonists, are useful clinically in intraoperative, postoperative and chronic pain applications to attenuate the respiratory depression and maintain the analgesic effects of mu opioid receptor analgesics.

5. On page 67, please replace the paragraph beginning at line 1, with the following paragraph:

Both fentanyl (a strong mu-receptor analgesic agent) and 3290W93 (a compound with mixed delta and mu receptor activity), whose chemical structure is shown below:



were found to produce high levels of analgesia. Results are depicted in Figures 2A and 2B.

6. On page 67, please replace the paragraph beginning at line 8, with the following paragraph:

M5 Figures 2A and 2B show comparative analgesic and respiratory depression effects of 3290W93 and fentanyl in rats. Effects are plotted at 4 (Fig. 2A) and 8 (Fig. 2B) minute time points at which peak effects were observed following drug administration. A greater separation between analgesic and